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A retrospective, observational study: early versus late favipiravir in COVID-19 pneumonia

COVID-19 pnömonisinde erken ve geç dönemde favipiravir: retrospektif gözlemsel bir çalışma

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ABSTRACT

Aim: Positive results have been reported regarding the early use of favipiravir,a RNA-dependent RNA polymerase inhibitor,in the COVID-19 pandemic. In our study, we aimed to understand the potential role of favipiravir in controlling COVID-19 pneumonia and sepsis by comparing the early use of favipiravir with the late using.

Material and Method: Treatments are carried out in line with the guidelines constantly updated by the Ministry of Health in Turkey. Following the guide published on April 14,2020,we examined 18 patients who received favipiravir as the last treatment option in the late period and 17 patients who received favipiravir in the early period in two different groups.We recorded the demographic characteristics,co morbidities,APACHE-II scores,consecutive SOFA scores and mortality status of the patients in both groups.

Results: The difference between groups in terms of gender and age was not statistically significant.The difference between groups in terms of APACHE-II score was statistically significant.(p=0.018)The late group also had higher APACHE-II scores.The difference between groups in terms of exitus was not statistically significant but lower in the group using favipiravir early.

Conclusion: In studies with a limited number of patients, favipiravir has been shown to have a significant advantage over lopinavir/ritonavir in viral clearance as well as a significant reduction in viral load when used in the early period.Similarly,in our study,patients who used favipiravir in the late period came to us more seriously and the mortality rate was higher. We think that favipiravir had a significant effect even in studies with a small number of patients, and larger studies are needed in this area.

Keywords: COVID-19, favipiravir, pneumonia

ÖZ

Amaç: COVID-19 pandemisinde RNA bağımlı bir RNA polimeraz inhibitörü olan favipiravirin erken kullanımına ilişkin olumlu sonuçlar bildirilmiştir. Çalışmamızda favipiravirin erken kullanımı ile geç kullanımı karşılaştırarak COVID-19 pnömonisi ve sepsis kontrolünde favipiravirin potansiyel rolünü anlamayı amaçladık.

Gereç ve Yöntem: Türkiye'de Sağlık Bakanlığı tarafından sürekli güncellenen kılavuzlar doğrultusunda tedaviler yürütülmektedir.14 Nisan 2020 tarihinde yayınlanan rehberin ardından geç dönemde son tedavi seçeneği olarak favipiravir almış 18 hastayı ve erken dönemde almış olan 17 hastayı iki farklı grupta inceledik. Her iki gruptaki hastaların demografik özellikleri, komorbiditeleri, APACHE-II skorları, ardışık SOFA skorları ve mortalite durumları kaydedildi.

Bulgular: Gruplar arası cinsiyet ve yaş farkı istatistiksel olarak anlamlı değildi. Gruplar arası APACHE-II puanı açısından fark istatistiksel olarak anlamlıydı (p=0.018). Geç dönemde kullanan grubun APACHE-II puanları daha yüksekti. Gruplar arasında mortalite oranı favipiraviri erken kullanan grupta istatistiksel olarak anlamlı olmasa da numerik olarak daha düşüktü.

Sonuç: Sınırlı sayıda hasta ile yapılan çalışmalarda, favipiravirin erken dönemde kullanıldığında viral klirenste lopinavir/ritonavire göre belirgin bir avantaj sağladığı ve viral yükte önemli bir azalma sağladığı gösterilmiştir. Favipiraviri geç dönemde kullanan grup bize daha ciddi geldi ve mortalite oranı daha yüksekti. Favipiravir az hasta sayılı çalışmalarda bile anlamlı bir etki yaptığı ve bu konuda yapılacak daha büyük çalışmalara ihtiyaç olduğunu düşünüyoruz.

Anahtar kelimeler: COVID-19, favipiravir, pnömoni

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INTRODUCTION

The coronavirus infection that started in Wuhan, China at the end of 2019 quickly surrounded the world and was declared as a pandemic by the World Health Organization (WHO) as of March 12, 2020 (1,2).

There is no specific drug that has a specially developed license against COVID-19. Testing available drugs provided an emergency treatment opportunity in the pandemic.Treatment options are very limited all over the world; Different combinations of 7 drugs thought to be effective have been genereally tried. (hydroxychloroquine, lopinavir/ritonavir, darunavir/ritonavir, oseltamivir, remdesivir, favipiravir) (1,3).

Favipiravir is a purine analog that inhibits RNA-dependent RNA polymerase (RdRP), which is required for viral replication in human cells. The drug is converted intracellularly into its active phosphorylated form and recognized as a substrate by the viral RdRP. When this enzyme which is necessary for the replication of viruses, is inhibited, a decrease in viral load occurs (4,5).

Tanaka et al. (6) demonstrated the beneficial effects of favipiravir use such as decrease in pulmonary viral load and decrease in tumor necrotizing factor (TNF) alpha levels in their study on influenza infections.

In a metanalysis investigating the side effects and safety profile of favipiravir, it was emphasized that it has a positive safety profile, it is well tolerated especially in short-term use, large-scale studies are needed to determine its long-term effects (7). It is necessary to be careful in terms of teratogenicity potential and hyperuricemia and QTc prolongation (8,9).

There are studies showing that the use of favipiravir as the first option in the early period in COVID-19 pneumonia is more effective in reducing the severity of sepsis and its response in late use is not effective (10).

In our study, we aimed to understand the potential role of favipiravir in the control of COVID-19 pneumonia and sepsis by comparing early and late period using

MATERIAL AND METHOD

The study was carried out with the permission of Eskişehir Osmangazi University Faculty of Medicine Non-Interventional Clinical Researchs Ethics Committee (Date: 14.07.2020, Decision No: 26). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Following the approval of the ethics committee and the Ministry of Health commission, polymerase chain reaction (PCR) positive COVID-19 pneumosepsis patients who were followed and treated in the Anesthesiology and Reanimation Intensive Care Unit during the pandemic period between 11.03.2020-01.06.2020 were included in the study. The patients in Turkey were treated in algorithms prepared by the ministry of health and continuously updated (11). In the first scientific committee guidelines, favipiravir is recommended for use in the relatively late period (as an alternative to lopinavir / ritanavir therapy) only in patients with severe pneumonia who do not respond to initial treatment regimens (hydroxychloroquine + oseltamivir + azithromycin (according to physician judgment)); It was included in the guide dated April 14, 2020 as the first treatment option in the early period in pneumonia cases. Patients before 14 April were included in the favipiravir-late group and after 14 April patients were included in the favipiravir-early group. In both groups, patients' ages, demographic data, comorbidities, acute physiology and chronic health evaluation-II (APACHE-II) scores, outpatient or hospital admission status, starting days of favipiravir treatment, number of days they received favipiravir treatment, adverse effects of favipiravir,discharge and mortality status were recorded. The consecutive sequential organ failure assessment (SOFA) scores of all patients were recorded and the effect of favipiravir on the treatment process and the severity of sepsis was evaluated. Patients with no consecutive SOFA scores were excluded from the study. Of the 52 patients who came with the suspicion of respiratory distress and coronavirus pneumonia, 17 patients with negative PCR tests were excluded, and the data of 35 patients in total were analyzed.

Statistical Analysis

Continuous variables are given by using; Mean, Standard deviation, Median, Minimum and Maximum values and categorical variables are shown by giving numbers and percentages. In the comparison of continuous varibles in 2 groups, Mann-Whitney-U test was used for non-normal distribution. Wilcoxon test was used to compare the values measured at 3 different times in the groups. Group comparisons of categorical variables were analyzed using crosstabs statistics (Chi-square tests: Pearson Chi-square. The values of the continuous variables measured at 3 different times were analyzed by General Linear Model in 2 groups. The statistical significance level was taken as $p < 0.05$.

RESULTS

Data of a total of 35 patients were analyzed, with data of 18 patients as late group and 17 patients as early group. The difference between groups in terms of gender and age was not statistically significant. The mean age was 74.14±12.55 ($p=0.577$). The difference between groups in terms of APACHE-II score was statistically significant. ($p=0.018$) The late group also had higher APACHE-II

scores. Only the difference between the groups in terms of hypertension was statistically significant and in the early group was seen at a higher rate ($p<0.05$). The difference between groups in terms of malignancy and DM was not statistically significant (**Table 1**). The difference between groups in terms of exitus was not statistically significant but lower in the group using favipiravir early (**Table 2**). Consecutive SOFA scores between favipiravir groups were not found to be statistically significant (**Table 3**). The most common adverse effect was hyperuricemia with 17 patients (%48.5).

Table 1 . Demographic characteristics of COVID-19 patients

	Patients, no. (%)All (35)	Favipiravir late group (n=18)	Favipiravir early group(n=17)	P value
Age, mean±SD, y	74.14±12.55	76.50±13.40	72.00±9.70	0.577
Gender	0.600			
Male	19	9	10	
Female	16	9	7	
Coexisting disorders				
Hypertension	23	9	14	0.044
Diabetes Mellitus	13	6	7	0.631
Malignancy	19	10	9	0.877
APACHE II	18.91±8.15	22.0±7.40	12.00±8.10	0.018

Table 2. Mortality status of COVID-19 patients

	Patients, no. (%) All (35)	Favipiravir late group (n=18)	Favipiravir early group(n=17)	P value
Mortality status	-	-	-	0.053*
Ex	24	15	9	-
Discharge	11	3	8	-

* Pearson Chi-square test.

Table 3 . Before and after threatment SOFA scores of the patients

	Favipiravir late group (n=18)		Favipiravir early group (n=17)	
SOFA-1	6.00±2.97		5.00±2.29	
SOFA-2	6.50±2.76		4.00±2.81	
SOFA-3	7.50±3.50		7.00±3.50	
Paired comparisons for SOFA scores in Favipiravir groups*				
	Z	P	Z	P
SOFA-2 vs SOFA-1	-1.038	0.299	-0.408	0.684
SOFA-3 vs SOFA-1	-2.079	0.007	-1.451	0.147
SOFA-3 vs SOFA-2	-2.509	0.012	-1.720	0.085

*Test:Wilcoxon Test

DISCUSSION

In our study, we evaluated the patients who were given favipiravir in the early and late periods in accordance with the algorithms in the guide, and we observed that the patients who were given favipiravir in the late period were hospitalized in intensive care with higher APACHE-II scores. Although it was not statistically significant, the mortality rate was higher in patients using favipiravir in the late period. Our results also support the hypothesis that early use of favipiravir is associated with more positive results.

Lopinavir / ritonavir compared to favipiravir in studies; favipiravir was shown to significantly reduce the mean time to viral clearance (12). Cai et al. (13) compared favipiravir and lopinavir / ritonavir for COVID-19 treatment in their study. In this study in which 35 patients were treated with favipiravir and 45 patients with lopinovir / ritonavir, favipiravir was independently associated with faster viral clearance and higher recovery rates on chest imaging 14 days after treatment. They also stated that favipiravir causes very rare side effects and is well tolerated by patients.

Preliminary results of the favipiravir study conducted by Ivashchenko et al. (14) have been published and they reported that favipiravir is significantly effective in viral clearance and is safely tolerated. In this manner the result of studies showing the effectiveness of favipiravir, the coronavirus treatment algorithms in Turkey also updated.

Studies have shown that the most common side effect is hyperuricemia (15). It has been theorized that it may be due to the inhibition of channel proteins responsible for uric acid excretion in the kidney (16). Controlled use has been recommended especially in cases such as gout and acute renal failure. In our study, hyperuricemia was observed in 48.5% of the patients .

Similar to our study, Doi et al. (17) evaluated the effects of early and late use of favipiravir in a study. The difference of the study was that they tried this in the newly diagnosed mild or asymptomatic patient groups. Almost no fever was reported in the group using early. Although not statistically significant, there was a numerical decrease in viral clearance. progression to severe pneumonia and exitus were not observed in any of the patients. Fujii et al. (18), similarly, showed that starting the drug in the earliest possible period after their study had a positive effect on the results.

The APACHE-II scoring system, which is the most widely used scoring system accepted in intensive care, is the most important predictive marker in determining the severity of the disease and mortality. In addition to the chronic diseases of the patients, APACHE-II calculates the hemogram, blood gas values, vital signs and electrolytes and estimated severity of the disease during admission (19). In our study, we examined patients with severe pneumonia requiring intensive care follow-up and we found that the group using favipiravir late comes with statistically significant higher APACHE-II scores. Although the mortality rate was not statistically significant, it was numerically higher in the group that used favipiravir in the late period.

To list the limitations of our study, the number of our patients was very low.Since we looked at it retrospectively, we only recorded the existing data. we only examined the

data of patients who needed intensive care follow-up. We do not have any data on how much favipiravir used in the early period protects patients from intensive care admission.

CONCLUSION

Patients using favipiravir in the late period came to us more severely and had a higher mortality rate. Favipiravir has an obvious effect even in studies with few patients, and larger studies are needed in this area.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Eskişehir Osmangazi University Medical Faculty Ethics Committee (Date: 14.07.2020, Decision No: 26).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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